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Original Research

Comparison of Optical Coherence Angiography Measurements in Patients with Neovascular and Non-Neovascular Age-Related Macular Degeneration

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Abstract

Objectives: The purpose of the study was to determine the differences of optical coherence tomography angiography (OCTA) measurements between the patients with neovascular age-related macular degeneration (AMD) and non-neovascular early AMD.

Methods: This retrospectively designed study included patients with neovascular AMD (N-AMD group) and non-neovascular early AMD (NN-AMD group). The patients had a completed ocular examination including best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg), and OCTA measurements such as choroidal blood flow (au) and retinal vessel density (VD, %).

Results: The N-AMD group (1.46±0.28 au) showed a lower mean choroidal flow measurement than the NN-AMD group (1.73±0.32 au), ($p<0.001$). The patients in the N-AMD group had reduced VD measurements in all superficial and deep retinal layers compared with the NN-AMD group. However, significant differences in VD measurements were observed only in total superficial parafovea and in the superior and inferior quadrants of superficial parafovea while comparing the N-AMD and NN-AMD groups ($p<0.05$ for all). Almost all deep retinal VD measurements ($p<0.05$ for them) were significantly different in the N-AMD group except the overall and foveal zones ($p=0.144$ and $p=0.433$, respectively).

Conclusion: Retinal VD is reduced in patients with N-AMD when compared to NN-AMD. This outcome offered a retinal vessel contribution to AMD pathogenesis.

Keywords: Neovascular age-related macular degeneration, Non-neovascular age-related macular degeneration, Optical coherence tomography angiography, Retinal vessel density

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Age-related macular degeneration (AMD) is one of the main causes of legal blindness and moderate-to-severe vision impairment worldwide, especially in the population aged 50 and over. In the past 30 years, the prevalence of blindness due to AMD has decreased by 30% on average. This decrease is thought to be related to the application of anti-vascular endothelial growth factor (anti-VEGF) treatments in exudative type AMD.[1] Neovascular type AMD (N-AMD) is characterized by the presence of choroidal neovascularization consisting of abnormal blood vessels of choroidal origin, and consequently, advanced macular degeneration leads to vision loss.[2] Abnormal vessels grow from the Bruch's membrane and extend under the retinal pigment epithelium (RPE) and/or into the subretinal space. Choroidal neovascularization in N-AMD may lead to photoreceptor damage and thus vision loss by causing bleeding,

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fluid exudation, and fibrosis.[2,3] In contrast to N-AMD, non-neovascular type AMD (NN-AMD) defines macular degeneration without choroidal neovascularization.

Optical coherence tomography angiography (OCTA) is a relatively new imaging device that combines the structural information of a standard optical coherence tomography (OCT) section through visualization of blood flow, providing high-resolution and three-dimensional data of different vascular layers. Thus, it enables high-quality imaging of the retinal and choroidal circulation without the need for dye injection.[3,4] When evaluated together with structural OCT sections, OCTA is an effective tool for both diagnosis and classification of N-AMD and has higher sensitivity and specificity than conventional methods such as fluorescein angiography or indocyanine green angiography.[4-6] Therefore, OCTA can help to make the right treatment decision and prevent unnecessary anti-VEGF injections by providing identification and classification of the choroidal neovascularization lesions.[4] In this study, we aimed to evaluate quantitative results of retinal and choroidal OCTA measurements in patients with N-AMD and early NN-AMD.

Methods

The study was conducted retrospectively and cross-sectionally at a tertiary eye clinic. Fully informed and written consent was obtained from all patients before the image acquisition. The study was adhered to the requirements of the Declaration of Helsinki and approved by the local ethics committee (Date: December 01, 2020, Number: 3022).

Study Protocol and Patient Selection

A total of 71 right eyes of 71 patients with N-AMD and NN-AMD were recircuited in the study. Thirty-three eyes of 33 patients with the clinical diagnosis of NN-AMD had type 2 choroidal neovascularization and served as the N-AMD group. The remaining 38 eyes of 38 patients with the clinical diagnosis of early NN-AMD comprised the NN-AMD group. The demographic (age and gender) and clinical data (lens status, previous intravitreal injections, follow-up time, ophthalmic examination findings, and ocular measurements including visual acuity, intraocular pressure, choroidal flow, and OCTA scans) were obtained from medical chart records. Patients with a definitive number of intravitreal injections were included in the N-AMD group. All patients underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg, non-contact pneumatic tonometry), anterior segment assessment with slit-lamp biomicroscope, dilated fundus examination, choroidal blood flow (au), and OCTA measurements. Clinical fundus characteristics of early NN-AMD patients included drusen and RPE abnormalities. Clinical fundus characteristics of N-AMD patients included neovascular derangement (choroidal neovascularization formation), subretinal fibrosis, and subretinal fluid or hemorrhage/hard exudate. Patients with high ametropia (spherical equivalent >−6 D, >+4D), media opacity, concomitant macular diseases other than AMD, previous vitreoretinal surgeries, geographic atrophy, non-AMD-related choroidal neovascularization, and poor-quality images were excluded from the study.

Measurement Protocol

An enhanced depth imaging and spectral-domain OCTA (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA, USA) was used for image acquisition. This commercially available, standard deviation (SD)-OCTA can perform 70,000 A-scans per second using fixation tracking software and a motion correction algorithm. Scans with significant artifacts (such as large floaters, segmentation errors, and blinking or motion artifacts) and signal strength lower than 7/10 were excluded and repeated till the appropriate scans were captured. The measurements were performed by the same experienced and masked technician. The scans were capture over a 3 × 3 mm area centered on the fovea. Superficial retinal vessel density (VD, %) measurement was automated segmented from the ILM to the inner plexiform layer (IPL) and deep retinal VD measurement was automated segmented from the IPL to the outer plexiform layer (Fig. 1). VD was quantified as the total number of pixels contributing to the blood flow signal detectable by OCTA. There are no vascular structures above the RPE level in healthy eyes. Therefore, OCTA is not expected to detect blood flow at

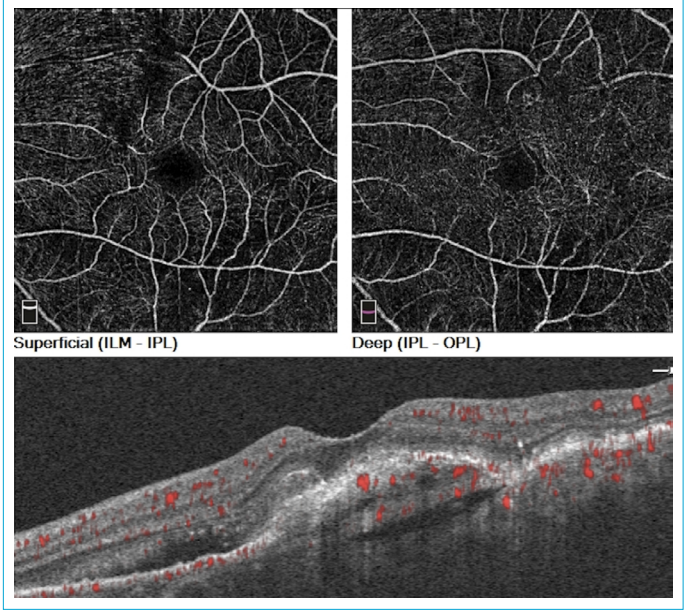

Figure 1. Vessel density measurements of superficial and deep retinal layers with associated segments using optical coherence tomography.

the level of the outer retinal layers. VD measurements were analyzed in overall, foveal, and parafoveal areas. Parafoveal measurements were assessed in the temporal, superior, nasal, and inferior quadrants.

Statistical Analysis

Statistical analyses of the data were performed using SPSS software (IBM Corp., NY, USA; version 22.0). Constant variables were expressed as the mean±SD. The Kolmogorov–Smirnov test was performed to assess the normal distribution. Parametric or non-parametric tests were used whether the data distribution is normal or not. Categorical variables were evaluated by the Chi-square test. The comparison of scale variables was performed using independent samples t-test or Mann–Whitney U-tests. The Pearson or Spearman tests were used for correlation analysis. P<0.05 was accepted as statistically significant.

Results

The NN-AMD group was slightly younger than the N-AMD group (p=0.045). There was not any statistical difference in the gender numbers of the patients between the N-AMD and NN-AMD groups (p=0.845). The NN-AMD group was less likely to be pseudo-phakic than the N-AMD group (42.1% vs. 57.6%, p=0.044). The numbers of the patients with controlled systemic hypertension and type 2 diabetes mellitus were similar in the N-AMD and NN-AMD groups (p>0.05 for both). The N-AMD and NN-AMD groups had similar mean follow-up duration (p=0.237). The N-AMD group presented with a poorer mean BCVA than the NN-AMD group (p<0.001). The N-AMD and NN-AMD groups had similar mean IOP measurements (p=0.304). The N-AMD group had a lower mean choroidal flow value than the NN-AMD group (p<0.001). All these data are represented in Table 1.

Overall, foveal, parafoveal (temporal, superior, nasal, and inferior quadrants) VD measurements obtained from superficial and deep retinal layers are represented in Tables 2 and 3, respectively. The N-AMD group presented with lower VD measurements in all superficial and deep retinal layers than the NN-AMD group. Significant differences in retinal VD measurements were noted only in the total superficial parafovea and in the superior and inferior quadrants of superficial parafovea between the N-AMD and NN-AMD groups (p<0.05 for all). Almost all deep retinal VD measurements (p<0.05 for them) showed significant differences between the groups except the overall and foveal assessments (p=0.144 and p=0.433, respectively).

Discussion

It is essential to assess the choroidal neovascularization lesions in detail for the diagnosis, treatment decision, and follow-up of N-AMD. Furthermore, in N- or NN-AMD, OCTA scans play an important role and provide benefits to elimi-

Table 1. Demographic and clinical features of the patients in the N-AMD and NN-AMD groups

Characteristics	N-AMD group (n=33)	NN-AMD group (n=38)	P*
Age (years)	73.69±10.17 (58–79)	65.03±7.79 (55–74)	0.045
Gender (n)			0.845
Female	19 (57.6%)	21 (55.3%)	
Male	14 (42.4%)	17 (44.7%)	
Lens Status (n)			0.044
Phakic	14	22	
Pseudo-phakic	19	16	
BCVA (in decimal)	0.18±0.09	0.64±0.25	<0.001
IOP (mmHg)	14.38±3.53	13.84±4.06	0.304
Choroidal flow (au)	1.46±0.28	1.73±0.32	<0.001
Systemic disease (n)			
Hypertension	8	6	0.372
Diabetes	6	5	0.222
Follow-up duration (years)	3.58±2.03 (1–5)	3.05±1.65 (1–4)	0.237
Intravitreal injection (n)			-
Bevacizumab	3.02±1.14 (0–7)	-	
Aflibercept	3.46±1.02 (0–7)		

AMD: Age-related macular degeneration, *the Chi-square and independent samples Student's t-tests were used, n: Number, BCVA: Best-corrected visual acuity, IOP: Intraocular pressure.

Table 2. The comparison of the superficial retinal vessel density measurements between the N-AMD and NN-AMD groups

VD measurements (%)	N-AMD group (n=33)	NN-AMD group (n=38)	P*
Superficial overall	40.59±7.07	43.05±4.20	0.085
Superficial fovea	20.82±9.92	21.61±6.45	0.354
Superficial parafovea	40.82±6.29	46.38±4.74	0.039
• Temporal quadrant	44.45±6.85	44.61±4.93	0.903
• Superior quadrant	42.06±7.74	47.32±5.16	0.045
• Nasal quadrant	42.09±8.76	44.10±4.98	0.231
• Inferior quadrant	41.07±7.42	47.91±5.33	0.034

AMD: Age-related macular degeneration, VD: Vessel density, *the independent samples Student's t-test was used.

Table 3. The comparison of the deep retinal vessel density measurements between the N-AMD and NN-AMD groups

VD measurements (%)	N-AMD group (n=33)	NN-AMD group (n=38)	P*
Deep overall	42.83±7.23	45.59±8.44	0.144
Deep fovea	31.45±12.69	33.48±8.24	0.433
Deep parafovea	45.30±7.23	50.18±3.96	0.001
• Temporal quadrant	44.70±8.52	51.18±4.11	<0.001
• Superior quadrant	45.03±9.54	49.67±4.64	0.014
• Nasal quadrant	44.43±11.30	50.73±4.18	0.002
• Inferior quadrant	42.33±10.59	49.77±4.85	0.001

CNV: Choroidal neovascular membrane, AMD: Age-related macular degeneration, VD: Vessel density, *the independent samples Student's t-test was used.

nate choroidal neovascularization lesions associated with non-vascularized macular drusen and drusenoid pigment epithelial detachment accompanied by subretinal fluid.[4,7,8] The development of OCTA has enabled segmental analysis of the retinal and choroidal vascular structures without dye injection.[9] Compared to fluorescein angiography, OCTA provides excellent quality images with high resolutions and more accurate three-dimensional visualization of the retinal and choroidal vasculature, especially in the deep layers.[10] Retinal VD may be affected in any type of AMD, but choroidal neovascularization is mainly located in the deep retinal vascular plexus, outer nuclear layer, ellipsoid zone, and choroid.[10] This study investigated the potential alterations in vascular plexuses for further understanding of the possible impact of vascular hemodynamic factors in the pathogenesis of AMD. In the present study, OCTA was used to examine and compare the superficial and deep retinal VD measurements in the N-AMD and NN-AMD groups. The results of the study demonstrated significantly lower VD measurements in almost all areas of the deep retinal layer, whereas VD measurements were significantly lower in certain areas of the superficial retinal layer in the N-AMD group compared with the NN-AMD group. Meanwhile, the N-AMD group represented mean poorer BCVA and lower choroidal flow values than the dry-AMD group.

It is known that the pathophysiology of AMD is complex and multifactorial, which is associated with genetics, age, and environmental conditions.[11] Choroidal vasculature alterations in AMD might be secondary to dietary aging, oxidative stress, fat intake, smoking, systemic hypertension, carotid, coronary, and peripheral vascular disorders causing atherosclerosis, loss of vascular compliance, and increased vascular stiffness, which are also known risk factors for the development and progression of AMD.[12,13] Choroidal vascular damage has been demonstrated in NN-AMD as well as the N-AMD.[14,15] Similar to our results, early laser Doppler flowmetry investigation showed decreased choroidal blood flow in the eyes of AMD patients.[16] Supporting our study, the histological investigations represented that vascular impairment of the choriocapillaris could precede the structural damage of RPE in choroidal neovascularization.[15] It has been documented that VEGF is essential to increase vascular permeability since it changes the blood-retina barrier, thereby affecting the exudation of the retina and choroid.

[17] The anti-VEGF injection can act on the retinal and choroidal vascularization, decrease their vascular permeability, exudation, and modify VD distribution.[18]

The influence of choroidal hemodynamics on the AMD pathogenesis has been well documented, but the impact of retinal vasculature on the AMD pathogenesis has remained unclear. Similar to our findings, a study showed that both superficial and deep retinal vascular layers changed in the late stages of AMD.[15] Moreover, the authors also observed a significant reduction in the mean superficial VD measurements of eyes with intermediate AMD, but not early AMD.[19] A study concluded that retinal VD measurements showed a reduction in intermediate AMD when compared to age-matched normal controls, but longitudinal alterations in retinal capillary plexus did not represent a correlation with drusen volume increase during 12 months.[20] A retrospective study reported that superficial retinal VD reduced in N-AMD when compared to NN-AMD, but anti-VEGF therapy did not have an impact on the VD measurements.[21]

The results of a study showed that the existence of the cilioretinal artery can prevent the development of N-AMD, but whether the artery traverses the center of the fovea did not affect this condition.[22] This suggests that macular retinal perfusion might have an important effect on the pathogenesis of AMD or CNV, but foveal center perfusion might not have such an important role. The findings of the present study representing similar superficial and deep foveal VD measurements in the N-AMD and NN-AMD groups support this situation.[21, 22]

The current study focused on the superficial retinal VD besides the deep retinal VD, because the VD measurements in the superficial retinal layer have been well established using the OCTA system and are less likely to be affected by the N-AMD pathologies located in the outer layers of the retina.[21, 23] The benefit of examining the superficial layers of the retina is abstinence of artifacts and poor signal quality related to drusen and other pathologies of AMD as well as the avoidance of shadowing actions that may affect the deeper layers of the retina while measuring VD using OCTA.[24] It has been also demonstrated that anti-VEGF injections impaired the deep retinal VD and the choriocapillaris, but not superficial VD in exudative AMD, indicating the requirement for more robust investigations of different layers of the retina.[25] However, various OCTA algorithms measure different borders for the segmentation of retinal layers, which might give different results in the VD measurements.[26]

Nonetheless, this study has some limitations, including a relatively small sample size, retrospective nature, and lack of choriocapillaris measurements. Due to the retrospective nature of our study, we could not hypothesize whether decreased retinal VD might increase the risk of NN-AMD progression to N-AMD development. Considering these limitations, new studies with larger sample sizes and the inclusion of choriocapillaris measurement should be conducted in future investigations.

Conclusion

Our results support the interesting opinion that the vasculature of the superficial retina might have an impact on the pathogenesis of the N-AMD and may enable prognostic data regarding the risk for the development and progression of the N-AMD.[17, 19-21, 25, 26] Regardless of the number of intravitreal injections, N-AMD lesions may cause a significant decrease additionally in certain areas of the superficial retinal layer besides the prominent reductions in all areas of the deep retinal layer. As expected, decreased blood flow and visual impairment were noted in the N-AMD group. To the best of our knowledge, this study might be among the limited reports demonstrating reduced superficial and deep retinal VD measurements in N-AMD patients when compared to NN-AMD patients.

Disclosures

Ethics Committee Approval: The study was adhered to the requirements of the Declaration of Helsinki and approved by the local ethics committee (Date: December 01, 2020, Number: 3022)

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.D.; Design – M.D., C.A.; Supervision – M.D.; Materials – E.B.A.O., Z.Y.; Data collection &/or processing – Z.Y., E.B.A.O.; Analysis and/or interpretation – T.U., C.A.; Literature search – C.A., T.U.; Writing – C.A.; Critical review – M.D.

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